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VALUE IN HEALTH

A Modeled Economic Evaluation Comparing Atomoxetine with Stimulant Therapy in the Treatment of Children with Attention-Deficit/Hyperactivity Disorder in the United Kingdom

Suzi Cottrell, PhD,[1] Dominic Tilden, MPH,[1] Paul Robinson, MSc,[1] Jay Bae, PhD,[2] Jorge Arellano, MSc,[3] Eric Edgell, PharmD,[2] Mike Aristides, MSc,[1] Kristina S. Boye, PhD[2]

[1]IMS Health, London, UK; [2]Eli Lilly and Co., Indianapolis, IN, USA; [3]Eli Lilly and Co., Basingstoke, UK

ABSTRACT

Objective: To estimate the cost-effectiveness of atomoxetine for children with attention-deficity/hyperactivity disorder (ADHD) in the United Kingdom compared with current alternatives.

Methods: An economic model with Markov processes was developed to estimate the costs and benefits of atomoxetine versus other current ADHD treatment options. The model evaluated atomoxetine in five patient subgroups according to treatment history and the existence of comorbidities precluding stimulant medication. The incremental cost per quality-adjusted life-year (QALY) was calculated for atomoxetine treatment algorithms compared with comparator algorithms. The Markov process incorporated 18 health states, representing a range of outcomes across all treatment options included in the algorithms. Utility values were derived from a survey of 83 parents of children with ADHD. The effectiveness and safety aspects of the treatment options were based on a thorough review of controlled clinical trials and other clinical literature, and validated by international experts. Costs and outcomes were estimated using Monte Carlo simulation over a 1-year duration, with costs estimated from the perspective of the National Health Service in England and Wales.

Results: For stimulant-naive patients, the incremental cost per QALY gained for the atomoxetine algorithm compared with immediate-release methylphenidate hydrochloride (MPH) was £15,224 (£13,241 compared with extended-release MPH). In the stimulant-exposed populations, the incremental cost per QALY for the atomoxetine algorithm was between £14,169 and £15,878. For patients contraindicated for stimulant therapies, the incremental cost per QALY was £11,523 and £12,370 for stimulant-naive and stimulant-exposed populations, respectively.

Conclusion: The economic evaluation showed atomoxetine is an effective alternative across a range of ADHD populations and offers value-for-money in the treatment of ADHD.

Keywords: ADHD, atomoxetine, cost-utility analysis, economic evaluation, Markov process, methylphenidate, Monte Carlo simulation.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurobiological disorder, the essential feature of which is a persistent pattern of inattention and/or hyperactivity–impulsivity at a level that is developmentally inappropriate [1]. Affected children commonly exhibit disruptive behavior in the classroom, underachieve academically, and tend to be discordant in relations with family members and peers. In the majority of cases, children with ADHD continue to display behavioral problems and symptoms of the disorder throughout adolescence and well into adulthood [2,3]. Difficulties associated with the disorder may have long-term negative consequences with respect to employment prospects, the forming of good relationships, and the risks of substance abuse, crime, and accidental injury [4–9]. In the United Kingdom, the estimated prevalence of ADHD among school-aged children is approximately 5% [10].

Guidance from the National Institute for Health and Clinical Excellence (2006) suggests that severe cases may be treated with stimulant medications if remedial measures alone prove insufficient [10]. By far the most widely used medication for ADHD is methylphenidate hydrochloride (MPH). Available as either an immediate-release (IR) or an extended-release (XR) formulation, this drug has been prescribed in more than 90% of severe cases diagnosed in the United Kingdom [11]. Dexamphetamine sulfate, another stimulant, available in the United Kingdom as an IR formulation (IR-DEX), is prescribed far less frequently, principally as a second-line therapy in the small number cases that are refractory to MPH.

Address correspondence to: Suzi Cottrell, IMS Health, Level 3, Lee House, 109 Hammersmith Road, London W14 OQH, UK. E-mail: scottrell@uk.imshealth.com

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Atomoxetine is an alternative to stimulants in the treatment of ADHD with once-a-day oral dosing. There is consistent evidence that atomoxetine is superior to placebo [12], although existing evidence does not allow for clear differentiation between atomoxetine and other treatments for ADHD on the grounds of clinical effectiveness in terms of standard measures of ADHD symptom control [13]. However, a placebo-controlled trial has been conducted to test morning and late-afternoon/evening ADHD symptom relief using a new, recently validated, parent-reported instrument (the Daily Parent Ratings of Evening and Morning Behavior, Revised [14]). Results suggest that, among those patients who respond to atomoxetine, a single dose each morning provides a lasting effect through to the following morning, provided that the medication is taken on a regular daily basis [15]. In contrast, the duration of efficacy of MPH may be more limited. A single dose of XR-MPH, or three repeated doses of IR-MPH, will provide approximately 12 hours of therapeutic coverage [16–18]. Consequently, based on their pharmacokinetic and pharmacodynamic characteristics and using usual dose regimens, it is unlikely that these drugs would provide therapeutic coverage through the night or at the time of waking.

The objective of the present study was to estimate the cost-effectiveness of using atomoxetine as a new treatment option for children with ADHD in the United Kingdom, to determine whether the extra benefits justify the extra cost of atomoxetine. The study was designed to stratify the comparisons by patient subgroups, taking into consideration the medication alternatives available to them, depending on prior treatment history and whether use of stimulants is contraindicated by coexisting conditions. The economic model was developed to compare the costs and benefits of treatment algorithms that include atomoxetine with current treatment algorithms for the management of ADHD. Results of the model are presented as the incremental cost per quality-adjusted life-year (QALY) for atomoxetine relative to current therapy for each patient population. A comparison of the costs and health outcomes predicted by the model is intended to aid decision-makers in determining whether to publicly fund atomoxetine therapy.

Methods

Patients and Populations

In recognition that 1) children with ADHD are frequently codiagnosed with one or more comorbidities [19], some of which are contraindicated for medication with stimulants [20], and 2) a patient's stimulant history is a determining factor in clinical outcomes [21,22], patients in the evaluation are segregated, according to their treatment history and contraindication status, into five mutually exclusive patient groups:

1. Stimulant-naive patients are patients with no history of pharmacotherapy use and no contraindications to stimulants.
2. Stimulant-failed patients are individuals who have been previously (prior to entry into the model) medicated with methylphenidate but have failed this therapy because of lack of efficacy or intolerable side effects.
3. Stimulant-averse patients are those who have experience of stimulant medication and have responded successfully but would like to stop their medication if a nonstimulant medication was available.
4. Stimulant-contraindicated patients (naïve) are patients who have no history of pharmacotherapy use but are precluded from using stimulant therapies because of a pre-existing contraindicated condition(s), including severe depression, marked anxiety, tics, a family history or diagnosis of Tourette's syndrome, known drug dependence or a history of drug dependence or alcoholism [20].
5. Stimulant-contraindicated patients (exposed) are those who have been previously treated with a stimulant therapy but are now precluded from using stimulant therapies because of one or more conditions—including severe depression, marked anxiety, tics, a family history or diagnosis of Tourette's syndrome, known drug dependence or a history of drug dependence or alcoholism —potentially developed while receiving stimulant therapy [20].

Patients who are currently successfully being treated with methylphenidate, and who are satisfied with this treatment, are excluded from the analysis because it is assumed that these patients are unlikely to switch medication.

Treatments and Comparators

The primary outcome of the analysis is to estimate the cost-effectiveness of atomoxetine based on the treatment algorithms available to, and commonly used by, each of the five patient populations. Accordingly, the model considers the four treatment options available in the United Kingdom, namely atomoxetine, MPH (XR and IR), dexamphetamine, and "no medication." Overall, we consider treatment strategy in the following order: atomoxetine, MPH (either XR or IR), dexamphetamine, and no treatment. Atomoxetine is considered as the first choice to allow the model fully to capture the potential effects of introducing atomoxetine to the United Kingdom. With respect to MPH, two formulations of MPH (XR and IR) are assumed similar enough to each other that if one formulation does not work for a patient, the other formulation

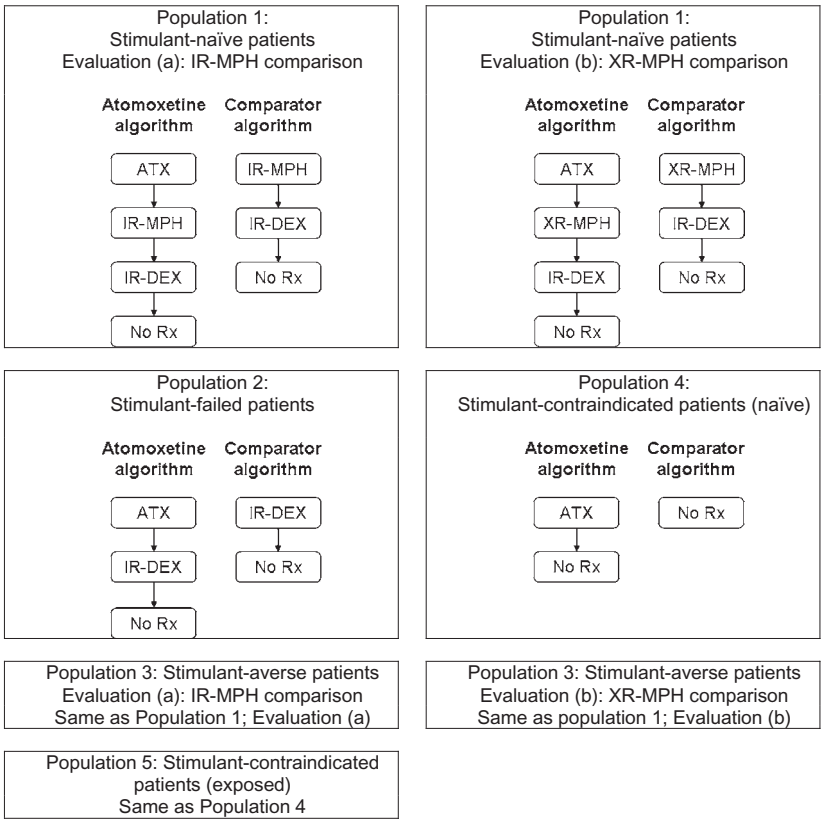

Figure 1 Treatment algorithms compared in the economic model, by patient population. For definitions of the patient populations, see Methods. [a]In populations 1 and 3, two evaluations were undertaken. Evaluation (a) in these populations refers to an analysis where IR-MPH is considered the stimulant therapy of choice. Evaluation (b) in these populations refers to an analysis where XR-MPH is considered the stimulant therapy of choice. ATX, atomoxetine; IR-DEX, immediate-release dexamphetamine sulfate; IR-MPH, immediate-release methylphenidate; XR-MPH, extended-release methylphenidate; Rx, medication.

will not be considered an alternative therapy. When contraindications and past stimulant failure are considered for each patient group, unique treatment strategies emerge for each group. Figure 1 summarizes the treatment algorithms, with and without atomoxetine, for each of the five patient populations.

Model Structure

An economic model, constructed using DATA Pro software [23], was developed to calculate and compare the costs and benefits of the various treatment algorithms, with and without atomoxetine, available to each patient population, using Monte Carlo simulations of a Markov process. The economic evaluation uses a cost-utility analysis to calculate the incremental cost per QALY gained by atomoxetine compared with the prevailing therapeutic options available in the United Kingdom.

The model uses a Monte Carlo simulation whereby a single patient is followed through the Markov process in monthly cycles over a period of 1 year. It was deemed inappropriate to extend the model beyond the time frame covered by the available clinical data. Instead, it is implicitly assumed that there is no difference in health benefits between the medications in the longer term. Costs and outcomes are accumulated as the patient advances through the cycles and 20,000 simulations are performed for each patient population to establish the mean costs and outcomes across all possible transitions through the Markov process (Fig. 2). These results are then used to calculate incremental cost-effectiveness ratios for each comparison in the different patient populations. Given that the model duration is within 1 year, costs and effects were not discounted. The Markov process used a half-cycle correction, which meant that patients were attributed their initial health state utility values half way through the first cycle.

Upon entering the Markov process, patients are distributed into one of four health states per treatment they receive, their response to that treatment, and occurrence of any adverse events associated with that treatment. Upon failure of therapy, patients move through to the next treatment option specified by that algorithm.

The 18 health states in which patients can reside cover all possible combinations of treatment-events that patients may experience. Patients remain within their resident health state until one of the following events occur.

1. The patient discontinues medication because of lack of efficacy—applicable only to patients on an active treatment and in a nonresponder health state. The model assumes a maximum of two consecutive nonresponse cycles. A third nonresponse cycle results in automatic discontinuation because

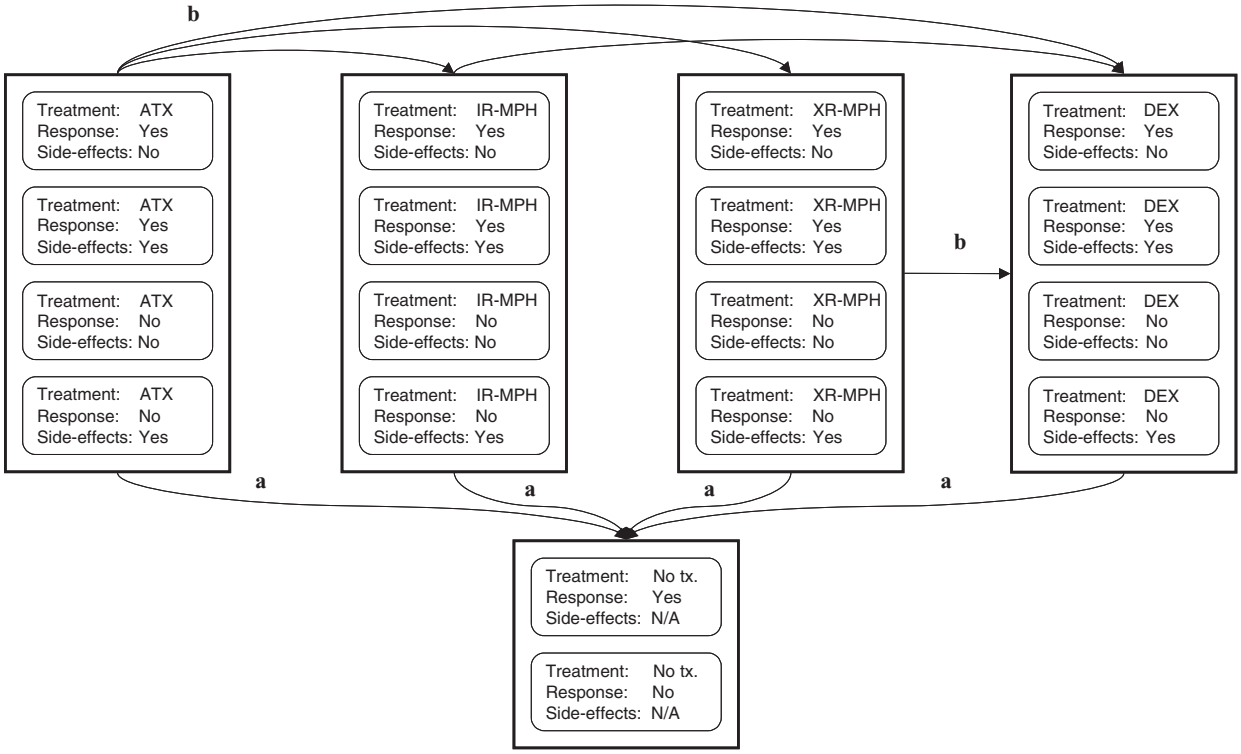

Figure 2 Structure of the Markov process used to estimate costs and outcomes of individual treatment options. [a]Represents transitions between health states where the patient is discontinuing pharmacotherapy. [b]Represents transitions between health states where the patient is starting a new pharmacotherapy (after discontinuing a previous pharmacotherapy). ATX, atomoxetine; DEX, immediate-release dexamphetamine sulfate; IR-MPH, immediate-release methylphenidate; N/A, not applicable; tx, treatment; XR-MPH, extended-release methylphenidate.

of lack of efficacy. After discontinuing one medication, the patient will switch immediately to the next alternative in the treatment algorithm to begin the next Markov cycle.

2. The patient discontinues medication because of a medication-related adverse event and progresses to the next line of therapy according to the treatment algorithm.
3. An adverse event resolves.
4. The patient discontinues medication for any other reason—applicable equally to all patients on active treatment. These patients are assumed to stop therapy altogether.
5. The patient relapses—applicable only to those patients in a responder health state. A patient who relapses becomes a nonresponder in the following Markov cycle.
6. The patient experiences a delayed response to medication (this possibility is examined only in a sensitivity analysis)—applicable only to those patients on an active treatment and in a nonresponder health state. A patient who experiences a delayed response becomes a responder in the following Markov cycle.

Although the structure of the Markov process is identical for each of the initial treatment options in the model, the distribution of patients across the health states and transition between health states depend on the treatment that the patient is receiving at any particular time. Parameters are dependent on health state and treatment line (e.g., the probability of response with atomoxetine is different in first- and second-line settings). Patients who discontinue medication altogether will move to one of the two "no medication" health states and remain in this health state for the duration of the model.

The model structure allows estimation of the expected costs and health outcomes for each treatment algorithm. Results are presented as the incremental cost per QALY gained of the introduction of atomoxetine for each of the patient populations.

Model Variables

Costs. Costs are estimated from the perspective of the National Health Service in England and Wales, and only study drug costs are included. This assumes that all nondrug health-care costs and indirect costs are equivalent between the treatment groups being compared. Such an assumption may be considered biased against the active therapies that have the potential to reduce symptoms and, consequently, a patient's

Table 1 Medication costs in the economic model

	Atomoxetine cost	IR-MPH cost	XR-MPH cost	IR-DEX cost
Average daily dose	1.1 capsules	25.46 mg*	32.75 mg*	13.11 mg*
Daily cost of medication	£2.15†	£0.47‡	£1.34‡	£0.18‡
Days on medication per Markov cycle	30	30	30	30
Cost of medication per Markov cycle	£64.35	£14.19	£40.05	£5.40

*Primary care data [24].
†Daily cost of atomoxetine is independent of average daily dose. Cost is based on a cost per capsule, independent of capsule strength [25] and accommodates 10% of patients requiring two rather than one capsule per day.
‡Daily costs of stimulants based on current costs [25] applied to the average daily dose, weighted by the relative days of therapy of each pack size for each medication. Figures are rounded to nearest £0.01.
IR-DEX, immediate-release dexamphetamine sulfate; IR-MPH, immediate-release methylphenidate; XR-MPH, extended-release methylphenidate.

reliance on health-care professionals. Furthermore, the cost of drugs associated with the treatment of medication-related side effects is not considered. Because of the persistence of insomnia, patients treated with stimulants (IR-MPH, XR-MPH, IR-DEX) are more likely than patients treated with atomoxetine to require medication for side effects, indicating that the exclusion of these costs may be biased against atomoxetine.

Cost variables used in the Markov process and their respective data sources are summarized in Table 1. The cost for atomoxetine, based on most patients' need for only a single capsule a day, independent of capsule strength, is £1.95. In the evaluation, however, the base case uses a more conservative daily cost of £2.15, assuming 10% of patients take two capsules to reach an optimal dose. Calculation of the daily cost of stimulant medications is based on the estimated average daily dose taken by patients [24] and the relative use of available pack sizes for each medication according to current market research. Unit costs of stimulant medication were derived from the UK edition of the *Monthly Index of Medical Specialities* [25]. Patients in the model receive 30 days of medication per monthly cycle.

Health State Utility Values

Health state utility values for 14 of the 18 possible health states included in the economic model were based on a utility valuation survey of 83 parents of children with ADHD in the United Kingdom using standard gamble methodology [26]. The health-state description consisted of four domains: 1) descriptors referring to behavior during different time periods throughout the day; 2) information concerning the child's overall social well-being; 3) attributes regarding medication regimen (e.g., frequency of administration); and 4) medication-related adverse events. Parents were chosen as the most suitable patient proxy respondents on the basis that many ADHD children within the target population would be too young to provide reliable responses. The survey did not include utility estimates for four health states associated with IR-DEX therapy. In each case, however, parity with IR-MPH has been assumed, based on clinical expert opinion.

The health state corresponding to the atomoxetine "responder without side effects" had the highest utility value (0.959). Health states corresponding to "responder without side effects" for XR-MPH and IR-MPH had utility values of 0.930 and 0.913, respectively. For each of the "no medication" health states, utility values of 0.880 were obtained from the "child's own health state" as given by a subgroup of 23 parents whose children were not currently receiving medication. When compared with the values obtained for the theoretical "no-medication" health states, the utility value obtained for the unmedicated child's own state was found to be lower than the range of the theoretical states (0.899–0.950), and very close to the "nonresponder without side effects" values for the three medications (0.878, 0.847, 0.861) derived from the same sample of 23 parents. It was deemed more appropriate to apply the "child's own health state" utility value given by the parents of unmedicated children to all unmedicated patients in the model. It is worth noting that the "child's own health state" utility value given by the remaining 60 parents whose children were medicated was 0.917. This value is similar to the values given for theoretical IR-MPH and XR-MPH responder health states (0.913, 0.904, 0.930, 0.912), thus providing reassurance that the "child's own health state" utility values are reliable. In the sensitivity analysis, a value of 0.934 (upper confidence limit) for nonmedication responders was tested. Table 2 presents the utility scores utilized in the economic model.

The utility values generated were applied to the appropriate health states within the model, regardless of contraindication status to stimulants of the patient population or the line of therapy within any treatment algorithm.

Transition Probabilities

Transition probabilities used to populate the Markov process and respective data sources are presented in Tables 3 and 4.

Probabilities that did not vary by patient population (Table 3), including probabilites of medication-related adverse events and discontinuations from

Table 2 Utility values derived from the utility valuation survey

Health state	N	Mean utility value	SD	95% CI
Medication with atomoxetine; responder without side effects	83	0.959	0.077	0.942–0.976
Medication with atomoxetine; responder with side effects	83	0.937	0.096	0.916–0.958
Medication with atomoxetine; nonresponder without side effects	83	0.902	0.133	0.873–0.931
Medication with atomoxetine; nonresponder with side effects	83	0.886	0.148	0.854–0.918
Medication with IR-MPH; responder without side effects	83	0.913	0.128	0.885–0.941
Medication with IR-MPH; responder with side effects	83	0.904	0.137	0.875–0.933
Medication with IR-MPH; nonresponder without side effects	83	0.889	0.154	0.856–0.922
Medication with IR-MPH; nonresponder with side effects	83	0.875	0.164	0.840–0.910
Medication with XR-MPH; responder without side effects	83	0.930	0.107	0.907–0.953
Medication with XR-MPH; responder with side effects	83	0.912	0.124	0.885–0.939
Medication with XR-MPH; nonresponder without side effects	83	0.898	0.130	0.870–0.926
Medication with XR-MPH; nonresponder with side effects	83	0.884	0.143	0.853–0.915
No medication; responder*	23	0.880	0.133	0.826–0.934
No medication; nonresponder*	23	0.880	0.133	0.826–0.934

*Utility values for "child's own health states."
CI, confidence interval; IR-MPH, immediate-release methylphenidate; SD, standard deviation; XR-MPH, extended-release methylphenidate.

treatment, were derived from placebo-controlled clinical trials for atomoxetine [27–34] and an indirect meta-analysis of safety data from randomized placebo-controlled and active comparator studies of atomoxetine and methylphenidate [35].

Medication-related adverse events were defined as any adverse event 1) found to be significant for atomoxetine in a pooled analysis of safety data from six pivotal randomized placebo-controlled trials [27–33]; 2) found to be significant for IR-MPH in a published

Table 3 Transition probabilities used in the Markov process that do not vary by patient population

	Probability by treatment option				
	Atomoxetine	IR-MPH	XR-MPH	IR-DEX	No medication
Probability of one or more medication-related adverse events*	0.129	0.129	0.129	0.129	0.000
Probability that a medication-related adverse event is insomnia†	0.000	0.460	0.460	0.460	NA
Probability that a medication-related adverse event, which is not insomnia, will persist from one Markov cycle to the next‡					
First four cycles	0.473	0.473	0.473	0.473	NA
Cycles thereafter	1.000	1.000	1.000	1.000	NA
Probability that insomnia will persist from one Markov cycle to the next§					
First four cycles	NA	0.953	0.953	0.953	NA
Cycles thereafter	NA	1.000	1.000	1.000	NA
Probability that a nonresponder discontinues because of lack of efficacy during a Markov cycle¶	0.0989	0.0989	0.0989	0.0989	NA
Probability that a patient discontinues because of medication-related adverse event during a Markov cycle**	0.1209	0.1209	0.1209	0.1209	NA
Probability that a patient discontinues for reasons other than lack of efficacy or a medication-related adverse event during a Markov cycle¶					
First four cycles	0.384	0.384	0.384	0.384	NA
Cycles thereafter	0.000	0.000	0.000	0.000	NA

*Probabilities based on post-hoc analyses of safety data pooled from six randomized placebo-controlled trials of atomoxetine versus placebo [27–33]. Assumption of parity between active treatments based on similar post hoc analyses of data from a limited open-label direct comparator study [40], supported by data from a double-blind randomized trial of atomoxetine and XR-MPH [42] where the proportions of patients experiencing one or more adverse event of any nature were not significantly different between the active treatments. Values are net of the placebo rate, meaning that the "no medication" probability is zero, by definition.
†The probability based on the relative risk (0.428) of insomnia (atomoxetine vs. IR-MPH), estimated in an indirect meta-analysis of safety data [35], applied to the risk of insomnia for atomoxetine (4.7%) derived from pooled analysis of safety data from six pivotal randomized placebo-controlled trials of atomoxetine [5,27], giving a rate of insomnia for IR-MPH of 4.7/0.428 = 11%. The model assumes that insomnia is experienced only as a result of taking medication. Therefore, the probability for placebo is not applicable (i.e., zero) and the probabilities for active treatments are net of the placebo rate (i.e., subtract 5.1%). As a consequence, the model assumes that patients on atomoxetine have no risk of medication-related insomnia. Patients on IR-MPH who experience insomnia will come only from the population who experience one or more adverse events as derived above. Therefore for "if adverse event, probability that insomnia included" = (11.0–5.1)/12.9 = 46%. Parity is assumed between the stimulant treatments [16,18,22,45,46].
‡Probabilities based on temporal course of treatment-emergent adverse events where weekly reports from patients treated with atomoxetine over 52 weeks imply that, for most patients, medication-related adverse events mainly occur early in the treatment and are likely to resolve within approximately 16 weeks. The probability of 0.473 ($0.05^{1/4}$) for the first four cycles with adverse event reflects a nominal 5% of patients in whom adverse events (that are not insomnia) persist over this duration of the Markov process. The duration of persistence of adverse events (that are not insomnia) is assumed to be similar for each medication.
§Probabilities based on a survey of six consultant child and adolescent psychiatrists [38]. Responses suggested that 82.5% of cases of stimulant-related insomnia would persist for more than 16 weeks. The model assumes that patients with stimulant-related insomnia that persists beyond four cycles will continue to have insomnia as long as they remain on treatment. The probabilities of 0.953 ($0.824^{1/4}$) for the first four cycles of the Markov process and 1.000 for cycles thereafter reflect this.
¶Probabilities based on discontinuation rates, regardless of treatment, from data pooled from seven randomized placebo-controlled trials of atomoxetine [27–34], adjusted for differences between trials with respect to duration of follow-up. Discontinuations due to lack of efficacy were assumed to occur in only the nonresponder population. In each case, parity is assumed between the active treatments.
**Probabilities based on discontinuation rates due to adverse events from data pooled from six pivotal randomized placebo-controlled trials of atomoxetine [27–33], adjusted for differences between trials with respect to duration of follow-up. Discontinuations due to adverse events were assumed to occur only in the population experiencing one or more medication-related adverse events and therefore were net of the placebo rate. In each case, parity is assumed between the active treatments.
IR-DEX, immediate-release dexamphetamine sulfate; IR-MPH, immediate-release methylphenidate; NA, not applicable; XR-MPH, extended-release methylphenidate.

Table 4 Transition probabilities used in the Markov process that vary by patient population

		Probability by treatment option				
	Patient population	Atomoxetine	IR-MPH	XR-MPH	IR-DEX	No medication
Probability of response to treatment	1. Stimulant-naive*	0.7051	0.7727	0.7727	NA	NA
	2. Stimulant-exposed (failure)†	0.6674	NA	NA	0.6674	0.3983
	3. Stimulant-exposed (averse)‡	0.6217	0.7003	0.7003	0.6217	0.3983
	4. Contraindicated, stimulant-naive§	0.6667	NA	NA	NA	0.4231
	5. Contraindicated, stimulant-exposed§	0.5273	NA	NA	NA	0.3478
Probability of relapse per 30-day period¶	1. Stimulant-naive	0.0206	0.0206	0.0206	NA	NA
	2. Stimulant-exposed (failure)	0.0257	NA	NA	0.257	0.0447
	3. Stimulant-exposed (averse)	0.0257	0.0257	0.0257	0.0257	0.3983
	4. Contraindicated, stimulant-naive	0.0206	NA	NA	NA	0.0387
	5. Contraindicated, stimulant-exposed	0.0257	NA	NA	NA	0.0447

*Probabilities of response in stimulant-naive patients in whom stimulants are not contraindicated are based on a meta-regression analysis [39] of response data from randomized active comparator trials of atomoxetine and methylphenidate (MPH) [27,28,40–43]. Assumption of parity between stimulants is based on head-to-head trials of IR-MPH and XR-MPH [16,18].

†Probabilities of response in MPH-exposed (failed) patients in whom stimulants are not contraindicated are based on responder rates in a crossover trial of IR-MPH and IR-DEX [22]. Parity is assumed for atomoxetine and IR-DEX in patients who have failed to respond to MPH. The probability of response for "no medication" is derived from factoring down the rate of IR-DEX responders in IR-MPH-failed patients by applying the relative risk of response for placebo versus atomoxetine for stimulant-naïve patients derived in the meta-regression analysis.

‡Probabilities of response in MPH-exposed (nonfailure) patients in whom stimulants are not contraindicated are based on a meta-regression analysis [39] of response data from randomized active comparator trials of atomoxetine and MPH [27,28,40–43]. Assumption of parity between stimulants is based on head-to-head trials of IR-MPH and XR-MPH and IR-MPH and IR-DEX [16,18,22,46]. Parity is assumed for atomoxetine and IR-DEX in patients who have been exposed to MPH. The probability of response for "no medication" is derived from factoring down the rate of IR-DEX responders in IR-MPH-failed patients by applying the relative risk of response for placebo versus atomoxetine for stimulant-naïve patients derived in the meta-regression analysis.

§Probabilities of response in stimulant-naïve and stimulant-exposed patients in whom stimulants are contraindicated are based on responder rates from a randomized placebo-controlled trial of atomoxetine in patients with tics or Tourette's syndrome [34].

¶Probability of relapse = $1 - [(1 - C)^{(1/E)}]$, where C = the proportion of patients relapsing and E = approximate total number of follow-up days, derived from a relapse prevention study [44,45], divided by the approximate number of days per Markov cycle. Parity is assumed between active medications.

IR-DEX, immediate-release dexamphetamine sulfate; IR-MPH, immediate-release methylphenidate; Stimulant-exposed, patients with attention-deficit/hyperactivity disorder (ADHD) who have previously tried and failed on MPH because of lack of response; Stimulant-naive, ADHD patients who have never been exposed to MPH, dexamphetamine, or any other stimulant medication; XR-MPH, extended-release methylphenidate; Failure/nonfailure, whether stimulant-exposed patients failed MPH or not.

quantitative meta-analysis of safety data from randomized controlled trials [36]; or 3) listed as very common (frequency ≥10%) for Ritalin® and/or Concerta® XL in Summary Product Characteristics [20]. Medication-related adverse events comprised appetite loss, stomachache, vomiting, somnolence, irritability, dizziness, fatigue, insomnia, headache, and nervousness.

Assumptions regarding the persistence of medication-related adverse events are based on long-term treatment data for atomoxetine [37], where weekly reports of adverse events, either as a first or a repeat occurrence, fell off with time to fairly constant low levels which, in many cases, are considered to be close to the baseline reporting of such adverse events. These data imply that for most patients, medication-related side effects mainly occur early on in the treatment and are likely to resolve within approximately 16 weeks.

Data concerning time to resolution for methylphenidate-related adverse events are not available. Because adverse events associated with methylphenidate are mostly considered mild and transient, the model assumes that, with one exception, the time to resolution for methylphenidate-related adverse events is the same as for atomoxetine. The exception to this is stimulant-associated insomnia, which can persist in a proportion of cases. The probability that medication-related insomnia persists in methylphenidate-treated patients is based on responses collected in a survey of consultant child and adolescent psychiatrists, all highly experienced in treating children with ADHD [38].

Probabilities of response and relapse vary by patient population (Table 4). The evidence base for these variables in each of the populations is described below.

Stimulant-naive patients. Probabilities of treatment response in patients naive to stimulants are derived from responder rates estimated in a meta-regression analysis [39] of patient-level data from five randomized active comparator trials of atomoxetine and methylphenidate [27,28,40–43].

Stimulant-failed patients. The probability of response to IR-DEX in stimulant-exposed patients who have failed on MPH is derived from a crossover study of IR-DEX and IR-MPH in which a subgroup who failed to respond to IR-MPH were found to respond to IR-DEX [22]. The definition of response used in this crossover study was not the same as that used in this model. Nevertheless, the responder rate for IR-MPH in the first phase of the crossover study was comparable to the responder rate for MPH in naive patients obtained in the aforementioned meta-regression analysis [39]. It was therefore considered reasonable to take the rate of response to IR-DEX in the subgroup that did not respond to MPH from this trial and use it in the model.

Data from a randomized trial of atomoxetine and MPH [43] have similarly suggested that a subgroup of

patients who fail to achieve a response with MPH achieve a response with atomoxetine. In the absence of evidence using comparable definitions of response, parity of probability of response is assumed between atomoxetine and IR-DEX in patients who have failed to respond to IR-MPH or XR-MPH.

For those patients for whom "no medication" is the only remaining option in their medication algorithm, the probability of response is derived from factoring down the rate of IR-DEX responders in patients who failed to respond to IR-MPH [22] by applying the relative risk of response for placebo versus atomoxetine for naive patients derived in the meta-regression analysis [39].

Stimulant-averse patients. The probability of response in the stimulant-averse population is derived from responder rates estimated for stimulant-exposed patients in the meta-regression analysis [39] in which all patients with history of stimulant use prior to enrollment in the clinical trials had responded to their medication. Therefore, these data constitute an appropriate evidence base for this patient population in the model who also have a history of stimulant use.

Stimulant contraindicated patients. Probabilities of treatment response in patients contraindicated for stimulants were derived from responder rates in stimulant-exposed and stimulant-naïve patients in a randomized placebo-controlled trial of atomoxetine conducted exclusively in an ADHD patient group who had been codiagnosed with tic disorder or Tourette's syndrome [34]. The limitation of this, of course, is that patients with tics or Tourette's syndrome constitute a subgroup of, rather than being representative of, the overall stimulant-contraindicated population. Nevertheless, in the absence of data from a more appropriate patient group, this is the best estimate available.

Probabilities of relapse were based on data for stimulant-naive and stimulant-exposed patients in a placebo-controlled relapse prevention trial of atomoxetine responders [44,45]. In the absence of comparative data, an assumption of parity is made between relapse rates for all active treatment and also between patients who are contraindicated for stimulants and those who are not.

For all transition probability variables, where applicable, the assumptions of parity between IR-MPH and XR-MPH and between IR-MPH and IR-DEX are based on data published from head-to-head trials of treatments [16,18,22,46,47].

Sensitivity analysis. Extensive sensitivity analyses were carried out on all cost, utility, and transition probability variables. Full details of the sensitivity analysis are available by contacting the authors. The results of key findings are presented in the Results section.

Results

The results of the economic model are summarized In Table 5. Overall, the results of the model suggest that improved health outcomes, translated into increased QALYs, are possible with a treatment algorithm including atomoxetine compared with an algorithm without atomoxetine. This result was consistent across the five populations evaluated.

For the stimulant-naive population (population 1), inclusion of atomoxetine in the treatment algorithm was associated with additional costs of £408.34 (compared with the IR-MPH algorithm; Evaluation A) or £265.71 (compared with the XR-MPH algorithm; Evaluation B) per patient. The additional cost of the atomoxetine algorithm in stimulant-failed patients (population 2) was £448.78. In the stimulant-averse patients (population 3), it was £373.79 (compared with the IR-MPH algorithm; Evaluation A) or £256.13 (compared with the XR-MPH algorithm; Evaluation B). In the patient populations with contraindications to stimulant therapy, the incremental cost of the atomoxetine algorithm was £480.94 in those naïve to stimulant therapies (population 4) and £395.98 in those with a history of stimulant use (population 5).

Patients in the atomoxetine treatment group experienced greater time with response and greater time on medication (results not shown). This, together with the higher utility value associated with a response to atomoxetine relative to the other therapies included in the model, translated into QALY gains for patients in the atomoxetine algorithm. The atomoxetine algorithm was associated with QALY gains of 0.027 (compared with the IR-MPH algorithm; Evaluation A) or 0.020 (compared with the XR-MPH algorithm; Evaluation B) in the stimulant-naive population. In the stimulant-failed population, the atomoxetine algorithm was associated with 0.030 additional QALYs. In the stimulant-averse patient population, the QALY gains were 0.024 and 0.018 for the IR-MPH (Evaluation A) and XR-MPH (Evaluation B) comparisons, respectively. For patients with contraindications, the QALY gains in the atomoxetine algorithm were 0.042 for stimulant-naïve patients and 0.032 for stimulant-exposed patients compared with no medication.

The incremental cost per QALY gained with atomoxetine varied from £11,523 in contraindicated stimulant-naïve patients (population 4) to £15,878 when compared with the IR-MPH algorithm in stimulant-averse patients (population 3; Evaluation A). This is an intuitive result because atomoxetine is most cost-effective in the patient group in which there are no pharmacotherapy alternatives currently available, and least cost-effective in the patient group who are responding to current therapies.

Results for the other populations were also intuitively consistent. The incremental cost per QALY of

Table 5 Total costs, QALYs and incremental cost-effectiveness estimated in the economic model by treatment group and patient population

Population	Cost per patient			QALYs per patient			Incremental cost per QALY gained
	Atomoxetine algorithm	Comparator algorithm	Difference	Atomoxetine algorithm	Comparator algorithm	Incremental	
Population 1: Stimulant-naive patients (Evaluation A: IR-MPH comparison)	£534.09	£125.76	£408.34	0.9308	0.9040	0.0268	£15,224
Population 1: Stimulant-naive patients (Evaluation B: XR-MPH comparison)	£599.78	£334.07	£265.71	0.9341	0.9140	0.0201	£13,241
Population 2: Stimulant-failed patients	£488.26	£39.48	£448.78	0.9268	0.8967	0.0300	£14,945
Population 3: Stimulant-averse patients (Evaluation A: IR-MPH comparison)	£493.05	£119.27	£373.79	0.9263	0.9028	0.0235	£15,878
Population 3: Stimulant-averse patients (Evaluation B: XR-MPH comparison)	£568.96	£312.83	£256.13	0.9301	0.9120	0.0181	£14,169
Population 4: Stimulant-contraindicated patients (naive)	£480.94	£0.00	£480.94	0.9217	0.8800	0.0417	£11,523
Population 5: Stimulant-contraindicated patients (exposed)	£395.98	£0.00	£395.98	0.9120	0.8800	0.0320	£12,370

IR-MPH, immediate-release methylphenidate; QALY, quality-adjusted life-year; Stimulant-exposed, patients with attention-deficit/hyperactivity disorder (ADHD) who have previously tried and failed on methylphenidate because of lack of response; Stimulant-naive, ADHD patients who have never been exposed to methylphenidate, dexamphetamine, or any other stimulant medication; XR-MPH, extended-release methylphenidate; Failure/nonfailure, whether stimulant-exposed patients failed methylphenidate or not.

atomoxetine was lowest in the patient groups with the fewest alternatives currently available. The incremental cost per QALY was £12,370 and £14,945 for the stimulant-contraindicated (exposed) population (population 5) and the stimulant-failed group (population 2), respectively. In the stimulant-naïve group (population 1), the incremental cost per QALY was £15,224 (compared with the IR-MPH algorithm; Evaluation A) or £13,241 (compared with the XR-MPH algorithm; Evaluation B). In the stimulant-averse group (population 3; Evaluation B), the incremental cost per QALY of atomoxetine compared with the XR-MPH algorithm was £14,169 (Table 5).

Sensitivity Analysis

A comprehensive range of univariate and multivariate sensitivity analyses were performed for uncertain model variables and assumptions (the results of which are available from the authors upon request). In general, the incremental cost per QALY gained in each population was insensitive to univariate changes in key clinical and cost variables. Nevertheless, the sensitivity analyses show that the utility values of the most populous health states are important determinants of the cost-effectiveness of atomoxetine.

Given the importance of the utility values to the results of the economic model, additional sensitivity analyses of the utility values were explored. The intention of these additional sensitivity analyses was to see how the results of the model are affected when differences between utility values of corresponding health states for all treatments are reduced or eliminated. That is, how will incremental cost-effectiveness ratios be affected by the systematic reduction in the difference between atomoxetine utility values and those of IR-MPH, XR-MPH, IR-DEX, and no treatment for each health state. This analysis was performed for stimulant-naive patients (population 1) versus IR-MPH or XR-MPH (results shown in Fig. 3).

The incremental cost per QALY gained was between £13,000 and £18,000 per QALY for the base-case analysis. When differences in the utility values between corresponding health states of different treatments were reduced to 75% of the value given in the utility survey, the results were between £17,000 and £24,000 per QALY. The incremental cost per QALY reached a range of £42,000 to £62,000 per QALY when differences in utilities are reduced to 25% of the original values. Finally, when differences in utilities are eliminated, the incremental cost per QALY ratio increases dramatically.

This sensitivity analysis shows that when differences in utility values between treatment groups are removed the incremental cost per QALY gained of atomoxetine rises to unacceptable levels. However, the modest increase in the cost per QALY when differences are reduced by up to 75% and the sound methodology used to derive the utility values [26] serve to minimize

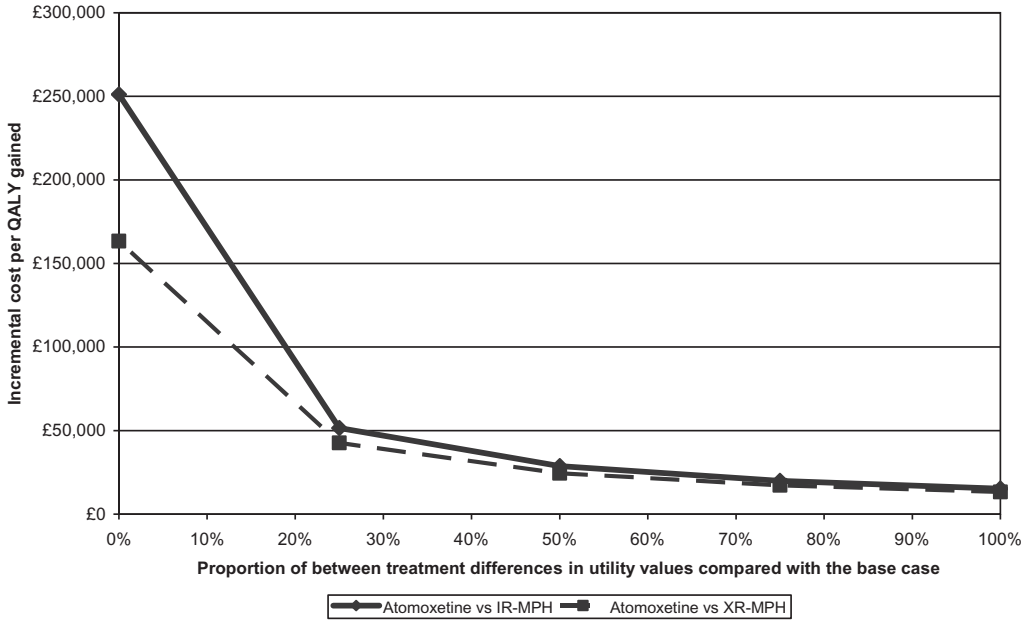

Figure 3 The incremental cost per QALY gained of atomoxetine under varying utility values used in the model. IR-MPH, immediate-release methylphenidate; QALY, quality of life years; XR-MPH, extended-release methylphenidate.

the uncertainty surrounding the utility values and thus maximize the reliability of the results of the base-case model.

Discussion and Conclusions

With new innovative technologies and pharmaceutical interventions developing alongside an increasing demand for improved health care, upward pressure on health-care costs is inevitable. With this in mind, payers must decide which technologies and interventions will provide best value-for-money. The quality of life gains associated with treatments can be quantified via cost-utility analysis, and such analysis plays a vital role in informing the decision-making process that determines which technologies or interventions should be funded. Cost-utility analysis is considered the most appropriate approach to the economic evaluation for the purpose of decision-making because QALYs are a final health outcome and are not disease-specific. This allows the quality of life gains from one intervention to be compared directly with those from interventions over a broad range of indications. Cost-utility analysis is particularly important in ADHD because of the variable nature of response and disease experience. Quality of life measures such as utility valuation are able to capture this variable nature in a way that traditional ADHD efficacy measures cannot.

This cost-utility analysis estimated that the incremental cost per QALY gained by inclusion of atomoxetine within the treatment algorithm was between £11,523 and £15,878, depending on the patient group and comparator algorithms. The results of the modeled economic evaluation and associated sensitivity analyses confirmed the utility values to be a key component in determining the cost-effectiveness of atomoxetine. Additionally, sensitivity analyses revealed a minimal impact of response rates, adverse events, and other transition probabilities.

Given that the utility values were a key factor influencing cost-effectiveness, it is important that users of this information have confidence in the data and do not consider this to be a weakness of the model. To this end, it should be noted that the utility values used in the evaluation were obtained from a utility valuation study of ADHD health states [26] that involved parents of children with ADHD living in the United Kingdom as the respondent population and used standard gamble methodology. In order to minimize any uncertainty or bias surrounding the utility values, the health states descriptors used in the study interviews were derived using robust methodology based largely on data from randomized clinical trials and validated by experts.

The clinical inputs to the economic model were primarily based on head-to-head randomized clinical trial evidence. In first-line patients, atomoxetine was found to be less efficacious than stimulant medications in terms of the number of patients responding to treatment. Nevertheless, there is evidence that patients responding to atomoxetine experience a more stable and longer-lasting response than those patients responding to stimulant therapies. Hence,

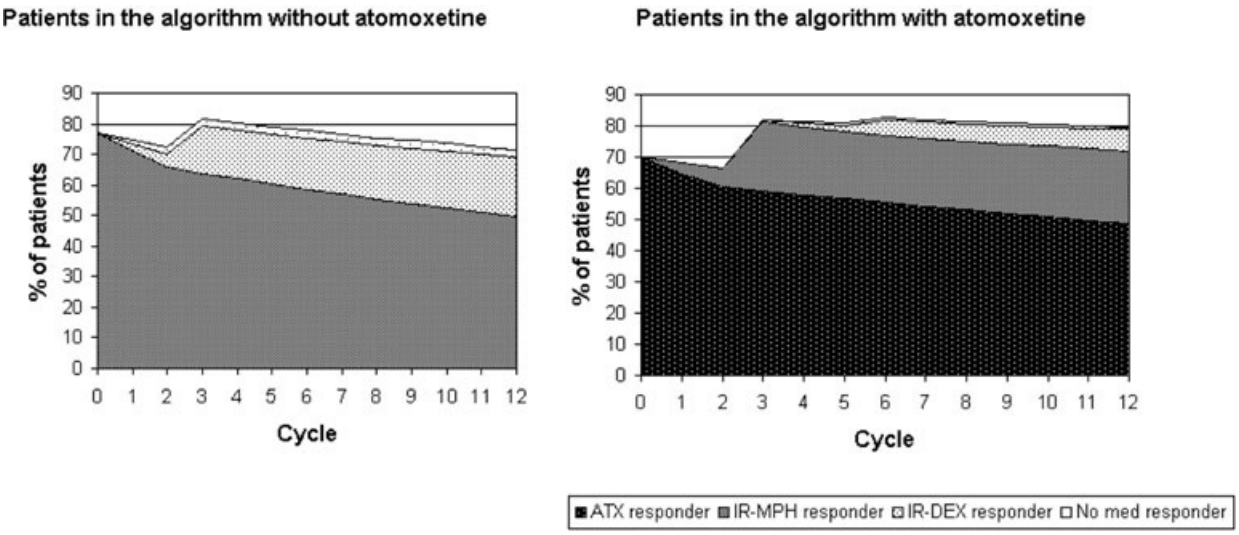

Figure 4 Proportion of population with response by cycle in each of the treatment algorithms (stimulant-naïve patients). ATX, atomoxetine; IR-DEX, immediate-release dexamphetamine sulfate; med, medication; IR-MPH, immediate-release methylphenidate.

the nature of response with atomoxetine, which was reflected in the health state descriptors used in the utility valuation study, is preferred to that of stimulant treatments.

A second advantage of atomoxetine treatment is that it represents an additional therapeutic option to patients with ADHD. Thus, it displaces, as opposed to replaces, current therapeutic options, resulting in an increase in the expected time on medication and an increase in the expected time with response (Fig. 4). This is also true for those patients who may be contraindicated to stimulant medications, where "no medication" would be the only alternative option.

As a consequence of these features, the lower rate of response for patients treated with atomoxetine compared with stimulant therapies is offset by an improved medication experience with atomoxetine that, in the context of the economic evaluation, leads to a greater number of QALYs overall.

It is recognized that there are several limitations to this study. First, it could be argued that a longer time frame may have been desirable to account for longer-term differences in costs and adverse effects of treatment. Nevertheless, any omissions due to the shorter time frame are likely to be conservative in that they bias the model generally against the active therapies, and more specifically against atomoxetine. For example, the model does not allow for the pattern of care of ADHD patients to change according to response to active therapy. This means the omission of nondrug costs within the model is assumed to be the same across all disease health states. Moreover, in an ideal situation, it would be preferable to have utility scores estimated from the patient perspective. Nevertheless, the use of parents of ADHD children as patient proxies is seen to provide the best practical alternative. An additional limitation is that the utilities were not collected in a head-to-head clinical trial. Rather the health states descriptors were derived from placebo-controlled clinical trial data and expert opinions, and utility values were subsequently collected through a standard gamble survey.

In conclusion, the results of this study show atomoxetine to be within the bounds of reasonable cost-effectiveness for the United Kingdom. The results of this analysis are considered robust, having been based on the best available clinical evidence, expert opinion, and a rigorously conducted utility valuation study of ADHD-related health states. Furthermore, the outcomes of this model demonstrate that consideration of response rates alone does not adequately describe the entire benefit of atomoxetine. The different nature of response between the treatments is also seen to be an important consideration for patients and parents, and the inclusion of a new therapeutic option adds to the quality of life for those patients who would have otherwise failed all treatment options.

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